REMARKS

This responds to the Office Action mailed on August 23, 2004. Claims 1-15 are pending in this application.

Personal Interview

Applicant wishes to thank the Examiner for extending the courtesy of a personal interview to Applicant's representative, Richard A. Schwartz, on December 15, 2004.

Applicant's representative pointed out that no document is of record that would equate the behavior of proteinoids and proteins. Specifically, no document is of record to indicate that proteinoids may be cross-linked. Without such a document the Mathiowitz and Margolin are improperly combined with Steiner, and no *prima facie* obviousness exists.

This account is believed to be a complete and accurate summary of the interview as required by 37 C.F.R. § 1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicants respectfully request that the Examiner point out any deficiencies in his next communication so that Applicants can amend or supplement the interview summary.

Information Disclosure Statement

Applicant respectfully requests that a copy of the 1449 Form, listing all references that were submitted with the Supplemental Information Disclosure Statement filed on July 28, 2003 and January 20, 2004 marked as being considered and initialed by the Examiner, be returned with the next official communication.

§103 Rejection of the Claims

Claims 1-15 were rejected under 35 USC § 103(a) as allegedly unpatentable over Steiner (U.S. Patent No. 4,925,673) in combination with Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606). According to the Examiner, while Steiner discloses encapsulation of pharmacological agents in proteinoid microspheres, and Mathiowitz discloses various methods for making protein microspheres, neither of these references teaches cross-linking of proteinoid microspheres with disulfide bridges. However, the Examiner asserts that

Margolin teaches use of reversible cross-linkers. Hence, according to the Examiner, claims 1-15 are obvious in view of this combination of references.

Claim 1 is directed to proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and crosslinked with a crosslinker that can form a pore upon exposure to a reducing agent.

The above rejections under 35 U.S.C. § 103(a), with respect to the references cited, are respectfully traversed. Applicants submit that Steiner teaches away from using cross-linking agents with proteinoid microspheres and neither of Mathiowitz or Margolin disclose or teach use of proteinoid microspheres with cross-linking agents. Moreover, even if one of skill in the art were motivated to cross-link the proteinoid microspheres of Steiner, such a modification would change the principle of operation of the Steiner microspheres, which is explicitly prohibited under M.P.E.P. § 2143.02. Hence, the combination of Steiner, Mathiowitz and Margolin do not teach the invention. Further facts and argumentation supporting this traversal is provided in more detail below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings to as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Failure to Disclose All Elements

Applicant submits that the references fail to disclose or teach all the claimed elements.

In particular, the Examiner has admitted that Steiner (U.S. Patent No. 4,925,673) is limited to disclosure of proteinoid microspheres that are not cross-linked. See Office Action at page 2 (August 23, 2004). In fact, the concept of adding a crosslinker to the proteinoid microspheres provided by Steiner would defeat the very purpose of the Steiner invention - to

permit release of a pharmacological agent from a proteinoid microsphere by dissolution. The principle by which the Steiner microspheres operate necessarily includes dissolution of the microspheres. See Steiner at col. 3, line 49 to col. 4, line 27. Nowhere does Steiner contemplate forming a pore in the microspheres upon exposure to a reducing agent. Hence, by reading the present invention (proteinoid microspheres that have a cross-linker that can form a pore upon exposure to a reducing agent) into the Steiner reference, the Examiner has impermissibly changed the operation of the reference. As stated in M.P.E.P. § 2143.02 a reference cannot render a claim obvious if the reference or combination of references would change the operation of the reference, for example, by requiring substantial reconstruction and re-design of the elements shown in the primary reference.

Mathiowitz (U.S. Patent No. 5,271,961) is irrelevant as prior art, because as admitted by the Examiner Mathiowitz does not teach cross-linking agent that can form pore upon exposure to a reducing agent. See Office Action at page 2 (Aug. 23, 2004). Also, Mathiowitz provides no teaching on proteinoid microspheres (made by thermal condensation of amino acids). Instead, Mathiowitz is limited to disclosure of methods for making protein microspheres by mixing a solution of proteins (not amino acids) and evaporating the solvent. Hence, Mathiowitz teaches no element of the claimed invention.

Moreover, there is no evidence of record that such protein microspheres have any of the physical or chemical properties of proteinoid microspheres. Thus, the teachings of Mathiowitz cannot be used to establish that cross-linking agents can or should be used with proteinoid microspheres. Mathiowitz does not cure the defects of Steiner or bridge any gap between the teachings of Steiner and those of Margolin.

Margolin (U.S. Patent No. 6,541,606) also provides no disclosure whatsoever of proteinoid microspheres. Instead, Margolin discloses methods for stabilizing biologically active macromolecules by crystallizing them from aqueous solutions using evaporation. See Abstract. There is no evidence of record that such biologically active macromolecules have any of the chemical or physical properties of proteinoid microspheres. Moreover, Margolin provides no disclosure of cross-linking with a cross-linker that can form a pore upon exposure to a reducing agent. Hence, Margolin fails to disclose all elements of the invention.

Therefore, each of the cited references is defective, as is the combination of references, because they fail to teach proteinoid microspheres made from amino acids that are cross-linked with a cross-linker that can form a pore upon exposure to a reducing agent.

No Reasonable Expectation of Success

One of skill in the art would not have a reasonable expectation of finding the present invention from the combination of Steiner (U.S. Patent No. 4,925,673), Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606), because none of these references teach using a crosslinking agent with a proteinoid microsphere or that such a linker can be cleaved in human serum. The Examiner appears to be relying upon Mathiowitz to establish a link between the proteinoid microspheres of Steiner and the cross-linking agents of Margolin. However, no such link exists because none of the references teach or suggest that proteinoid microspheres can or should be cross-linked. Hence, the combination of references cited by the Examiner provides no reasonable expectation of success.

Applicant submits that one of skill in the art would not have a reasonable expectation of success of producing the present invention by combining the teachings of Mathiowitz and Margolin with Steiner, because Steiner does not disclose cross-linking agents and both Mathiowitz and Margolin are limited to a disclosure of microspheres or crystals formed from the active agent, i.e., the protein or macromolecule of interest. Hence, while one of skill in the art may choose to cross-link an active agent, such a skilled artisan would not expect that cross-linking the shell of a microsphere would produce a microsphere that could release an encapsulated active agent. Certainly, the combination of cited references do not disclose or teach cross-linking the shell of a microsphere.

The present application teaches that a pore can form in the claimed microsphere upon exposure to a reducing agent and, surprisingly, that serum is a sufficiently reducing environment to permit such pore formation (see, e.g., Example 3 of the present invention). While one of skill in the art may choose to crosslink biologically active molecules as taught by Margolin, absent a teaching that such linkage should or can be used with proteinoid microspheres, and that such a cross linked microsphere can form a pore under physiological conditions, no one of skill in the art would contemplate use of cross-linking agents with proteinoid microspheres. Hence, one of

skill in the art would not be motivated to try to use crosslinking agents with proteinoid microspheres or have a reasonable expectation that such crosslinking agents would be successful with proteinoid microspheres, to thereby generate a microsphere that can form a pore in the microsphere upon exposure to a reducing agent.

Moreover, given that the conditions used for making microspheres from amino acids (thermal condensation) are so different from those used by Margolin and Mathiowitz (evaporation of solvent), one of skill in the art would have no reasonable expectation that the teachings on cross-linking agents provided by Margolin and Mathiowitz would be successful when making proteinoid microspheres from amino acids.

No Motivation to Combine

Applicant submits that there is no motivation to combine the teachings of Steiner (U.S. Patent No. 4,925,673), with those of Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606). Steiner is the only reference disclosing proteinoid microspheres made of amino acids (which is required by claim 1). The proteinoid microspheres described by Steiner are not cross-linked. Instead, Steiner relies upon acid/base dissolution of the proteinoid microspheres for release of a pharmacological agent. See Steiner at col. 3, line 61 to col. 4, line 27. One of skill in the art would understand that such crosslinking agents can inhibit the dissolution of the microspheres and thereby inhibit release of the pharmacological agent from the proteinoid microsphere of Steiner. Hence, one of skill in the art would not be motivated to combine the teachings of Steiner with the teachings on crosslinking agents by Mathiowitz and Margolin. Instead, one of skill in the art would conclude that such a combination would change the principle of operation the Steiner proteinoid microspheres, which is forbidden under M.P.E.P. § 2143.02. Hence, there is no motivation to combine the proteinoid microspheres of Steiner with the crosslinking agents of Mathiowitz or Margolin.

Similarly, one of skill in the art would not be motivated to combine the teachings of Mathiowitz and Margolin with Steiner, because both Mathiowitz and Margolin are limited to a disclosure of microspheres or crystals formed from the active agent, i.e., the protein or macromolecule of interest. Hence, one of skill in the art would not seek guidance on proteinoid microspheres from Mathiowitz or Margolin, because neither of these references discloses

anything about proteinoid microspheres that are made of amino acids and that can be used to encapsulate, but do not comprise, an active agent.

Hence, one of skill in the art would not be motivated to combine the teachings of Steiner, Mathiowitz and Margolin.

Therefore, Applicant submits that the combination of Steiner (U.S. Patent No. 4,925,673), Mathiowitz (U.S. Patent No. 5,271,961) and Margolin (U.S. Patent No. 6,541,606) does not produce the claimed invention. Applicant requests withdrawal of this rejection under 35 USC § 103(a) of claims 1-15.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date December 20, 2004 By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop AF, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 20 day of December, 2004.

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